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(54) Title: HISTIDINE AND HOMOHISTIDINE DERIVATIVES AS INHIBITORS OF PROTEIN FARNESYLTRANSFERASE

(57) Abstract

Novel inhibitors of protein farnesyltransferase enzyme are described, as well as methods for the preparation and pharmaceutical compositions of the same, which are useful in controlling tissue proliferative diseases, including cancer and restenosis.

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HISTIDINE AND HOMOHISTIDINE DERIVATIVES AS INHIBITORS OF PROTEIN FARNESYLTRANSFERASE

FIELD OF THE INVENTION

The present invention pertains to a number of compounds which can be used in the medicinal field to treat, prophylactically or otherwise, uncontrolled or abnormal proliferation of human tissues. More specifically, the present invention pertains to a number of compounds which act to inhibit the farnesyltransferase enzyme that has been determined to activate ras proteins which in turn activate cellular division and are implicated in cancer and restenosis.

BACKGROUND OF THE INVENTION

Ras protein (or p21) has been examined extensively because mutant forms are found in 20% of most types of human cancer and greater than 50% of colon and pancreatic carcinomas (Gibbs J.B., Cell, 65:1 (1991), Cartwright T., et al., Chimica. Oggi., 10:26 (1992)). These mutant ras proteins are deficient in the capability for feedback regulation that is present in native ras and this deficiency is associated with their oncogenic action since the ability to stimulate normal cell division can not be controlled by the normal endogenous regulatory cofactors. The recent discovery that the transforming activity of mutant ras is critically dependent on post-translational modifications (Gibbs J., et al., Microbiol. Rev., 53:171 (1989)) has unveiled an important aspect of ras function and identified novel prospects for cancer therapy.

In addition to cancer, there are other conditions of uncontrolled cellular proliferation that may be related to excessive expression and/or function of native ras proteins. Post-surgical vascular restenosis is such a condition. The use of various surgical revascularization techniques such as saphenous vein bypass grafting, endarterectomy and transluminal coronary angioplasty is often accompanied by complications due to uncontrolled growth of neointimal tissue, known as restenosis. The biochemical causes of restenosis are poorly understood and numerous growth factors and protooncogenes have been implicated (Naftilan A.J., et al., Hypertension, 13:706 (1989) and J. Clin. Invest., 83:1419; Gibbons G.H., et al., Hypertension, 14:358 (1989); Satoh T., et al., Mollec. Cell. Biol., 13:3706 (1993)). The fact that ras proteins are known to be involved in cell division processes makes them a candidate for intervention in many situations where cells that are dividing uncontrollably. In direct analogy to the inhibition of mutant ras related cancer, blockade of ras dependant processes has the potential to reduce or eliminate the inappropriate tissue proliferation associated with restenosis, particularly in those instances where normal ras expression and/or function is exaggerated by growth stimulatory factors.

Ras functioning is dependent upon the modification of the proteins in order to associate with the inner face of plasma membranes. Unlike other membrane-associated proteins, ras proteins lack conventional transmembrane or hydrophobic sequences and are initially synthesized in a cytosol soluble form. Ras protein membrane association is triggered by a series of post-translational processing steps that are signaled by a carboxyl terminal amino acid consensus sequence that is recognized by protein

farnesyltransferase (PFT). This consensus sequence consists of a cysteine residue located four amino acids from the carboxyl terminus, followed by two lipophilic amino acids and the C-terminal residue. The sulfhydryl group of the cysteine residue is alkylated by farnesyl-pyrophosphate in a reaction that is catalyzed by protein farnesyltransferase. Following prenylation, the C-terminal three amino acids are cleaved by an endoprotease and the newly exposed alpha-carboxyl group of the prenylated cysteine is methylated by a methyl transferase. The enzymatic processing of ras proteins that begins with farnesylation enables the protein to associate with the cell membrane. Mutational analysis of oncogenic ras proteins indicate that these post-translational modifications are essential for transforming activity. Replacement of the consensus sequence cysteine residue with other amino acids gives a ras protein that is no longer farnesylated, fails to migrate to the cell membrane and lacks the ability to stimulate cell proliferation (Hancock J.F., et al., Cell, 57:1617 (1989), Schafer W.R., et al., Science, 245:379 (1989), Casey P.J., Proc. Natl. Acad. Sci. USA, 86:8323 (1989)).

Recently, protein farnesyltransferases (PFTs, also referred to as farnesyl proteintransferases (FPTs) have been identified and a specific PFT from rat brain was purified to homogeneity (Reiss Y., et al., Bioch. Soc. Trans., 20:487-88 (1992)). The enzyme was characterized as a heterodimer composed of one alpha-subunit (49kDa) and one beta-subunit (46kDa), both of which are required for catalytic activity. High level expression of mammalian PFT in a baculovirus system and purification of the recombinant enzyme in active form has also been accomplished (Chen W.-J., et al., J. Biol. Chem., 268:9675 (1993)).

In light of the foregoing, the discovery that the function of oncogenic ras proteins is critically dependent on their post-translational processing provides a means of cancer chemotherapy through inhibition of the processing enzymes. The identification and isolation of a protein farnesyltransferase that catalyzes the addition of a farnesyl group to ras proteins provides a promising target for such intervention. Recently, it has been determined that prototypical inhibitors of PFT can inhibit ras processing and reverse cancerous morphology in tumor cell models (Kohl N.E., et al., Science, 260:1934 (1993), James G.L., et al., Science, 260:1937 (1993), Garcia A.M., et al., J. Biol. Chem., 268:18415 (1993)). Thus, it is possible to prevent or delay the onset of cellular proliferation in cancers that exhibit mutant ras proteins by blocking PFT. By analogous logic, inhibition of PFT would provide a potential means for controlling cellular proliferation associated with restenosis, especially in those cases wherein the expression and/or function of native ras is overstimulated.

PCT Application WO91/16340 discloses cysteine containing tetrapeptide inhibitors of PFT of the Formula CAAX.

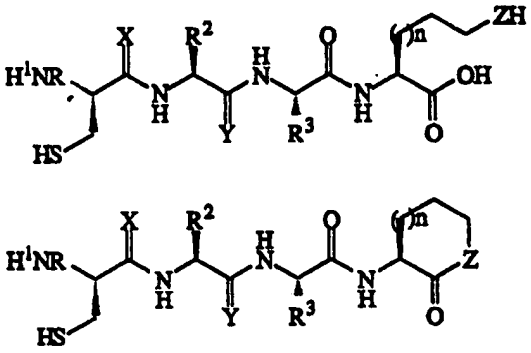
European Patent Application 0461869 discloses cysteine containing tetrapeptide inhibitors of PFT of the Formula Cys-Aaa^1-Aaa^2-Xaa.

European Patent Application 0520823 discloses cysteine containing tetrapeptide inhibitors of PFT of the Formula Cys-Xaa^1-dXaa^2-Xaa^3.

European Patent Application 0523873 discloses cysteine containing tetrapeptide inhibitors of PFT of the Formula Cys-Xaa^1-Xaa^2-Xaa^3.

European Patent Application 0528486 discloses cysteine containing tetrapeptide amides inhibitors of PFT of the Formula Cys-Xaa^1-Xaa^2-Xaa^3-NRR^1.

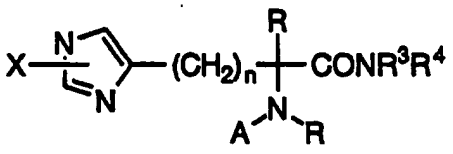
European Patent Application 0535730 discloses pseudotetrapeptide inhibitors of PFT of the following two formulas:



Compounds disclosed in the above references do not disclose or suggest a novel combination of structural variations found in the present invention described hereinafter.

SUMMARY OF THE INVENTION

Accordingly, the present invention is a histidine or homohistidine derivative of Formula I,



I

wherein:

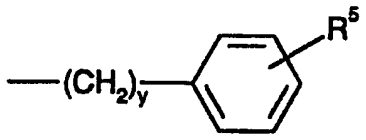
n = 1 or 2;

A = COR^2, CO_2R^2, $CONHR^2$, CSR^2, $C(S)OR^2$, $C(S)NHR^2$, or SO_2R^2 with R^2 as defined below;

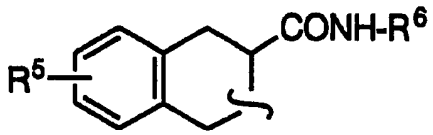
R = independently H or Me;

R^2 = alkyl, $(CH_2)_m$-cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heteroaryl with m = 0, 1, 2, or 3;

R^3 and R^4 = independently



or $(CH_2)_nCONH\text{-}R^6$ with y = 1-5 and n as defined above and with R^5 and R^6 as defined below, or R^3 and R^4 are connected together to form a ring of the following type:



with R^5 and R^6 as defined below, or $(CH_2)_x\text{-}R^7$, with x = 2-5, and R^7 as defined below;

R^5 = R^2, OR^2, or SR^2 with R^2 as defined above;

R^6 = $(CH_2)_nR^5$, $(CH_2)_nCO_2R^2$, $(CH_2)_nCONHR^2$, $(CH_2)_nCONH(CH_2)_{n+1}R^5$, $CH(COR^8)(CH_2)_nR^5$, with n, R^2, and R^5 as defined above and R^8 as defined below;

R^7 = $(CH_2)_m$-cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heteroaryl, $O(CH_2)_m$-cycloalkyl, $O(CH_2)_m$-aryl, $O(CH_2)_m$-heteroaryl with m = 0, 1, 2, or 3;

R^8 = OH, O-alkyl, NH_2, or NH-alkyl; and

X = H, Me, $(CH_2)_nCO_2R^9$, or $(CH_2)_nP(O)(OR^9)_2$, with R^9 = H or alkyl;

or a pharmaceutically acceptable salt thereof.

The present invention is also directed to the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, to inhibit the activity of a

protein farnesyltransferase enzyme as a method for treating tissue proliferative diseases.

A further embodiment of the present invention is the use of a pharmaceutical composition including a therapeutically effective amount of Formula I, or a pharmaceutically acceptable salt thereof, as a method for the treatment of cancer.

A still further embodiment of the present invention is the use of a pharmaceutical composition including a therapeutically effective amount of Formula I, or a pharmaceutically acceptable salt thereof, as a method for the treatment of restenosis.

A still further embodiment of the present invention is a pharmaceutical composition for administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in unit dosage form in the treatment methods mentioned above.

A final embodiment of the present invention pertains to methods for the preparation of compounds of Formula I, or pharmaceutically acceptable salts thereof, by solid phase synthesis, solution phase synthesis, and simultaneous multiple syntheses using a Diversomer® apparatus.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the compounds of Formula I, the term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like.

The term "cycloalkyl" means a saturated hydrocarbon ring which contains from 3 to 7 carbon

atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, and the like.

The term "aryl" means an aromatic ring which is a phenyl, 5-fluorenyl, 1-naphthyl, or 2-naphthyl group, unsubstituted or substituted by 1 to 3 substituents selected from alkyl, O-alkyl and S-alkyl, OH, SH, F, Cl, Br, I, CF_3, NO_2, NH_2, $NHCH_3$, $N(CH_3)_2$, NHCO-alkyl, $(CH_2)_mCO_2H$, $(CH_2)_mCO_2$-alkyl, $(CH_2)_mSO_3H$, $(CH_2)_mPO_3H_2$, $(CH_2)_mPO_3(alkyl)_2$, $(CH_2)_mSO_2NH_2$, and $(CH_2)_mSO_2NH$-alkyl wherein alkyl is defined as above and m = 0, 1, 2, or 3.

The term "heteroaryl" means a heteroaromatic ring which is a 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl, 2-, 3-, or 4-pyridyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl group, substituted or unsubstituted by 1 or 2 substituents from the group of substituents described above for aryl.

The following table provides a list of abbreviations and definitions thereof used in the present invention.

TABLE OF ABBREVIATIONS

Abbreviation*	Amino Acid
Ala	Alanine
Arg	Arginine
Asn	Asparagine
Asp	Aspartic acid
Cys	Cysteine
Glu	Glutamic acid
Gln	Glutamine
His	Histidine

* If the optical activity of the amino acid is other than L(S), the amino acid or abbreviation is preceded by the appropriate configuration D(R) or DL(RS).

TABLE OF ABBREVIATIONS (cont'd)

Abbreviation*	Amino Acid
Ile	Isoleucine
Leu	Leucine
Lys	Lysine
Met	Methionine
Phe	Phenylalanine
Pro	Proline
Ser	Serine
Thr	Threonine
Trp	Tryptophan
Tyr	Tyrosine
Val	Valine

Abbreviation*	Modified and Unusual Amino Acid
Aaa-CO_2R	An amino acid ester, for examples: Gly-CO_2Bn is Glycine, benzyl ester; Ser(OBn)-CO_2Me is O-Benzyl-serine, methyl ester.
(N-R)Aaa	(N-Me)His is N(α)-methyl-histidine; (N-(4-BnO-Bn)Gly is N-(4-phenyl-methoxybenzyl)-glycine.
Aaa-CONHR	An amino acid amide, for examples: Gly-CONHBn is Glycine, N-benzyl amide; Ser(OBn)-CONHEt is O-Benzyl-serine, N-ethyl amide; Tyr(OBn)-$CONHCH_2CH_2OBn$ is O-Benzyl-tyrosine, N-(2-(phenylmethoxy)-ethyl)amide;

* If the optical activity of the amino acid is other than L(S), the amino acid or abbreviation is preceded by the appropriate configuration D(R) or DL(RS).

TABLE OF ABBREVIATIONS (cont'd)

Abbreviation*	Modified and Unusual Amino Acid (cont'd)
	Cbz-His-CON(CH_2CH_2OBn)$_2$ is N(α)-phenylmethoxycarbonyl-histidine, N,N-bis-(2-phenylmethoxyethyl)amide.
Hcy	Homocysteine
Bal	Beta-alanine (or 3-aminopropionic acid)
His(1-Me)	1-Methyl-histidine (or N(τ)-Methyl-histidine)
His(Tr)	1-Triphenylmethyl-histidine (or N(τ)-Trityl-histidine)
Ser(OBn)	O-Benzyl-serine
Thr(OBn)	O-Benzyl-threonine
Tic	1,2,3,4-Tetrahydro-3-isoquinoline-carboxylic acid
Tyr(OBn)	O-Benzyl-tyrosine
(α-Me)Tyr(OBn)	2-Amino-3-(4-benzyloxyphenyl)-2-methyl-propionic acid (or α-Methyl-O-benzyl-tyrosine)
(N-Me)Tyr(OBn)	N-Methyl-O-benzyl-tyrosine

Abbreviation	Protecting Group
Ac	Acetyl
Ada	1-Adamantyl acetic acid
Adoc	Adamantyloxycarbonyl
Bn	Benzyl

* If the optical activity of the amino acid is other than L(S), the amino acid or abbreviation is preceded by the appropriate configuration D(R) or DL(RS).

TABLE OF ABBREVIATIONS (cont'd)

Abbreviation	Protecting Group (cont'd)
MeBn	4-Methylbenzyl
Cbz	Benzyloxycarbonyl
2-Br-Cbz	ortho-Bromobenzyloxycarbonyl
2-Cl-Cbz	ortho-Chlorobenzyloxycarbonyl
Bom	Benzyloxymethyl
Boc	tertiary Butyloxycarbonyl
Dnp	2,4-Dinitrophenyl
For	Formyl
Fmoc	9-Fluorenylmethyloxycarbonyl
NO_2	Nitro
Tos	4-Toluenesulfonyl (tosyl)
Tr	Triphenylmethyl (trityl)

Abbreviation	Solvents and Reagents
HOAc	Acetic acid
CF_3SO_2H	Trifluoromethanesulfonic acid
DCM	Dichloromethane
DCC	N,N'-Dicyclohexylcarbodiimide
DIC	N,N'-Diisopropylcarbodiimide
DIEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	N,N'-Dimethylformamide
EDAC	N-Ethyl-N'-Dimethylaminopropyl-carbodiimide
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
HCl	Hydrochloric acid
HF	Hydrofluoric acid
HOBT	1-Hydroxybenzotriazole
KOH	Potassium hydroxide
MeCN	Acetonitrile
MeOH	Methanol
NMP	N-Methylpyrrolidone

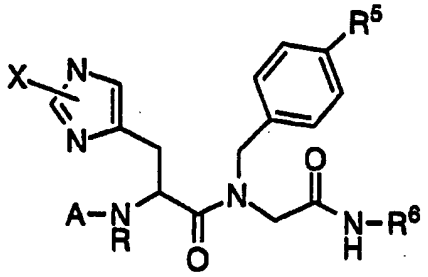
TABLE OF ABBREVIATIONS (cont'd)

Abbreviation	Solvents and Reagents (cont'd)
NHOS	N-Hydroxysuccinimide
iPrOH	iso-Propanol
TFA	Trifluoroacetic acid

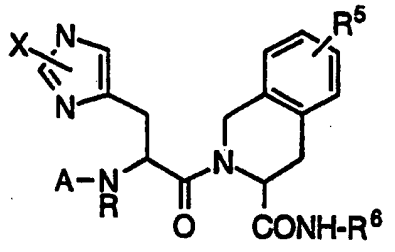
Abbreviation	Solid Phase Peptide Synthesis Resins
HMP Resin	4-(Hydroxymethyl)-phenoxymethyl-polystyrene resin
MBHA Resin	Methylbenzhydrylamine resin
PAM Resin	4-(Hydroxymethyl)-phenylacetamido-methyl-polystyrene resin
2-Cl-Tr Resin	2-Chlorotrityl-polystyrene resin
NH_2-Rink Resin	4-(Amino-(2',4'-dimethoxyphenyl)-methyl)-phenoxymethyl-polystyrene resin
Wang Resin	4-(Hydroxymethyl)phenoxymethyl-polystyrene resin

Abbreviation	Biological Reagents
FPP	Farnesyl pyrophosphate
PFT	Protein farnesyltransferase
DTT	Dithiothreitol
BSA	Bovine serum albumin

Preferred compounds of the invention are of Formulas II and III,



II



III

wherein:

A is limited to CO_2R^2, $CONHR^2$, $C(S)OR^2$, or $C(S)NHR^2$ with R^2 as defined below;

R = H or Me;

R^2 is limited to alkyl, $(CH_2)_m$-cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heteroaryl, with m = 0, 1, 2, or 3;

R^5 is limited to $(CH_2)_m$-aryl, $O-(CH_2)_m$-aryl, or $O-(CH_2)_m$-heteroaryl with m as defined above;

R^6 is limited to CH_2-R^5, $CH_2CO_2R^2$, CH_2CONHR^2, with n = 1 or 2, and with R^5 and R^2 as defined above; and

X is limited to H or Me;

or a pharmaceutically acceptable salt thereof.

The most preferred compounds of the invention are of Formula II and III, wherein:

A is further limited to CO_2R^2 or $CONHR^2$, with R^2 as defined below;

R is limited to H;

R^2 is further limited to alkyl, or $(CH_2)_m$-aryl with m = 0, 1, 2, or 3;

R^5 is further limited to $(CH_2)_m$-aryl or $O-(CH_2)_m$-aryl with m as defined above;

R^6 is limited to CH_2-R^5 or CH_2CONHR^2, with n = 1 or 2, and with R^5 and R^2 as defined above; and

X is limited to H or Me;

or a pharmaceutically acceptable salt thereof.

The present invention is also directed to the use of a compound of Formulas II and III, or a pharmaceutically acceptable salt thereof, to inhibit the activity of a protein farnesyltransferase enzyme as a method for treating tissue proliferative diseases.

A further embodiment of the present invention is the use of a pharmaceutical composition including a therapeutically effective amount of Formulas II

and III, or a pharmaceutically acceptable salt thereof, as a method for the treatment of cancer.

A still further embodiment of the present invention is the use of a pharmaceutical composition including a therapeutically effective amount of Formulas II and III, or a pharmaceutically acceptable salt thereof, as a method for the treatment of restenosis.

A still further embodiment of the present invention is a pharmaceutical composition for administering a therapeutically effective amount of a compound of Formulas II and III, or a pharmaceutically acceptable salt thereof, in unit dosage form in the treatment methods mentioned above.

A final embodiment of the present invention pertains to methods for the preparation of compounds of Formulas II and III, or pharmaceutically acceptable salts thereof, by solid phase synthesis, solution phase synthesis, and simultaneous multiple syntheses using a Diversomer® apparatus.

GENERAL METHODS FOR THE PREPARATION, EVALUATION AND USE OF COMPOUNDS OF FORMULA I

The compounds of Formula I may be prepared according to the synthetic strategy described in Scheme I. The secondary amine derivatives may be prepared by a reductive amination of an appropriate aldehyde with an appropriate amine in the presence of a reducing agent such as sodium triacetoxyborohydride. The secondary amine may then be coupled in the presence of an activating agent such as DCC and HOBT to a histidine derivative suitably functionalized at the N-terminus.

Scheme I

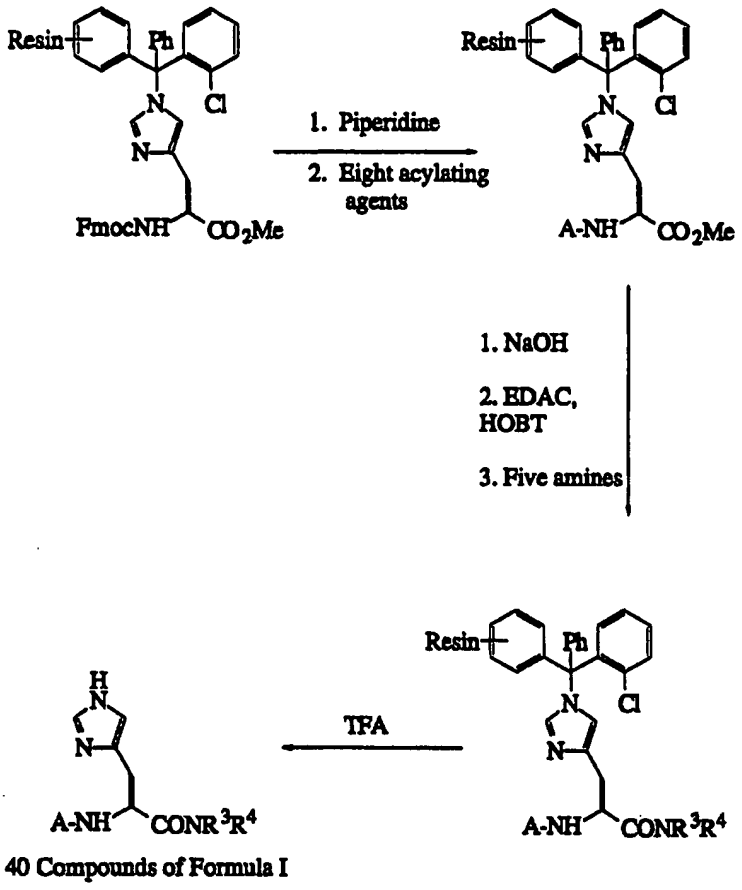
Additionally, compounds of Formula I may be prepared by simultaneous multiple solid phase syntheses using the Diversomer® apparatus described by DeWitt S.H., et al., Proc. Natl. Acad. Sci. USA, 90:6909 (1993). For example (Scheme II below), Fmoc-His-OMe is linked to 2-Cl-Tr resin using a sterically hindered amine such as DIEA as an HCl scavenger, the Fmoc protecting group is removed with piperidine, the resulting free amino terminus is acylated with a series of isocyanates, activated esters, acid chlorides and the like, the ester is saponified, the resulting carboxylic acid is activated with a carbodiimide reagent such as EDAC, DCC, or DIC, the activated carboxyl group is reacted with alcohols such as HOBT, NHOS or pentachlorophenol to give an activated ester, the activated ester is reacted with a series of amines and the resulting array of compounds of Formula I is cleaved from the resin by with hot HOAc or by treatment with TFA in DCM at room temperature. An alternative Diversomer® method (Scheme III) uses N(1) or N(3)-carboxymethyl-Fmoc-His-OMe which is linked to either Wang resin or 2-Cl-Tr resin. The remainder of the synthesis parallels that described in Scheme II.

For all three synthetic methods described above, appropriate consideration is given to protection and deprotection of reactive functional groups and to the sequence of synthetic steps. Knowledge of the use of common protecting groups and strategy for the assembly of complex organic molecules are within the usual realm of expertise of a practitioner of the art of organic

chemistry (see, for example, Greene T.W. and Wuts P.G.M., Protective Groups in Organic Chemistry, John Wiley and Sons (1991); Corey E.J. and Cheng X.-M., The Logic of Chemical Synthesis, John Wiley and Sons (1989)).

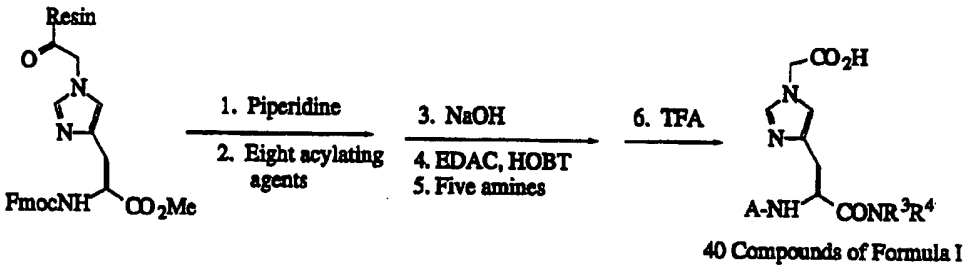
The homogeneity and composition of the resulting compounds is verified by HPLC, capillary electrophoresis, thin layer chromatography (TLC), proton nuclear magnetic resonance spectrometry (NMR), fast atom bombardment mass spectrometry (FAB-MS) and electrospray mass spectrometry (ES-MS).

SCHEME II: Multiple Simultaneous Synthesis Method



40 Compounds of Formula I

SCHEME III: Alternate Multiple Simultaneous Method



40 Compounds of Formula I

As discussed above, the compounds of Formulas I-III are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formulas I-III include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate, n-methyl glucamine (see, for example, Berge S.M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 66:1-19 (1977)).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. Preferably a compound of Formulas I-III can be converted to an acidic salt by treating with an aqueous solution of the desired acid,

such that the resulting pH is less than 4. The solution can be passed through a C18 cartridge to absorb the compound, washed with copious amounts of water, the compound eluted with a polar organic solvent such as, for example, methanol, acetonitrile, and the like, and isolated by concentrating under reduced pressure followed by lyophilization. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner or as above. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M., et al., "Pharmaceutical Salts", Journal of Pharmaceutical Science, 66:1-19 (1977)).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. Preferably, a compound of Formulas I-III can be converted to a base salt by treating with an aqueous solution of the desired base, such that the resulting pH is greater than 9. The solution can be passed through a C18 cartridge to absorb the compound, washed with copious amounts of water, the compound eluted with a

polar organic solvent such as, for example, methanol, acetonitrile and the like, and isolated by concentrating under reduced pressure followed by lyophilization. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner or as above. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

The PFT inhibitory activity of compounds of Formulas I-III was assayed in 30 mM potassium phosphate buffer, pH 7.4, containing 7 mM DTT, 1.2 mM $MgCl_2$, 0.1 mM leupeptin, 0.1 mM pepstatin, and 0.2 mM phenylmethylsulfonyl fluoride. Assays were performed in 96 well plates (Wallec) and employed solutions composed of varying concentrations of a compound of Formula I in 100% DMSO. Upon addition of both substrates, radiolabeled farnesyl pyrophosphate ([1-^{3}H], specific activity 15-30 Ci/mmol, final concentration 0.12 μM) and (biotinyl)-Ahe-Tyr-Lys-Cys-Val-Ile-Met peptide (final concentration 0.1 μM), the enzyme reaction was started by addition of 40-fold purified rat brain farnesyl protein transferase. After

incubation at 37°C for 30 minutes, the reaction was terminated by diluting the reaction 2.5-fold with a stop buffer containing 1.5 M magnesium acetate, 0.2 M H_3PO_4, 0.5% BSA, and strepavidin beads (Amersham) at a concentration of 1.3 mg/mL. After allowing the plate to settle for 30 minutes at room temperature, radioactivity was quantitated on a microBeta counter (Model 1450, Wallec). Compounds of Formulas I-III show IC_{50} values of 0.5 to 1000 nM in this assay and are thus valuable inhibitors of protein:farnesyltransferase enzyme which may be used in the medical treatment of tissue proliferative diseases, including cancer and restenosis.

The compounds of the present invention can be prepared and administered in a wide variety of oral, rectal and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formulas I-III or a corresponding pharmaceutically acceptable salt of a compound of Formulas I-III.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents,

flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 100 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as inhibitors of PFT, the compounds utilized in the pharmaceutical methods of this invention are administered at the initial dosage of about 0.01 mg to about 20 mg per kilogram daily. A daily dose range of about 0.01 mg to about 10 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide

Step 1: (4-Benzyloxybenzylamino)acetic acid methyl ester

To a mixture of glycine methyl ester hydrochloride (2.07 g, 16.5 mmol) and 4-benzyloxybenzaldehyde (3.18 g, 15.0 mmol) in CH_2Cl_2 (50 mL) at 0°C was added sodium triacetoxyborohydride (3.81 g, 18.0 mmol). The mixture was allowed to warm to room temperature and stirred for 4 hours. Aqueous $NaHCO_3$ was added and the mixture was stirred for 30 minutes. The aqueous layer was extracted three times with CH_2Cl_2. The combined

organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (75% EtOAc/hexane) gave 1.98 g (46%) of the title compound as a white solid, mp 57-58°C.

Step 2: N-[N-[(Phenylmethoxy)carbonyl]-L-histidyl]-N-[[4-(phenylmethoxy)phenyl]methyl]glycine methyl ester

To a suspension of CBZ-histidine (1.22 g, 4.21 mmol) in DMF (10 mL) was added HOBT hydrate (0.77 g, 5.05 mmol) and DCC (1.04 g, 5.05 mmol). The amine from Step 1 above (1.20 g, 4.21 mmol) was then added and the mixture was stirred at room temperature overnight. The mixture was filtered, and the filtrate was diluted with $CHCl_3$, washed twice with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Flash chromatography gave 1.68 g (72%) of the title compound as a white foam; ES-MS 557 (m + 1).

Step 3: N-[N-[(Phenylmethoxy)carbonyl]-L-histidyl]-N-[[4-(phenylmethoxy)phenyl]methyl]glycine

To a solution of the ester from Step 2 (1.53 g, 2.75 mmol) in THF (15 mL) and H_2O (5 mL) at 0°C was added LiOH hydrate (0.14 g, 3.30 mmol) and the solution was stirred 5 hours at 0°C. The solution was concentrated, the residue taken up in H_2O, and the pH was adjusted to 4-5 with 1N HCl. The resulting mixture was concentrated and dried in vacuo to afford 1.65 g of the title compound as a white solid;
FAB-MS 543 (m + 1).
Anal. calcd. for $C_{30}H_{30}N_4O_6 \cdot 1.2\ LiCl \cdot 2.0H_2O$:
C, 57.24; H, 5.44; N, 8.90.
Found: C, 57.35; H, 5.32; N, 8.62.

Step 4: N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]-methyl]glycinamide

To a solution of the acid from Step 3 (2.9 g, 5.33 mmol) in DMF (15 mL) was added HOBT hydrate (0.98 g, 6.39 mmol) and DCC (1.32 g, 6.39 mmol) followed by 2-benzyloxyethylamine hydrochloride (1.0 g, 5.33 mmol). Et_3N (0.82 mL, 5.86 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was filtered and the filtrate was diluted with $CHCl_3$, washed twice with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Flash chromatography (2-5% MeOH/$CHCl_3$) gave 2.25 g (63%) of the title compound as a white foam; ES-MS 676 (m + 1).

EXAMPLE 2

N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-[2-(1H-indol-3-yl)ethyl-N^2-[[4-(phenylmethoxy)phenyl]methyl]glycin-amide

According to Example 1, Step 4, by substituting tryptamine hydrochloride for 2-benzyloxyethylamine hydrochloride, the title compound was obtained as a white foam; ES-MS 685 (m + 1).

EXAMPLE 3

N-[N-[N-[(Phenylmethoxy)carbonyl]-L-histidyl]-N-[[4-(phenylmethoxy)phenyl]methyl]glycyl]glycine phenyl-methyl ester

According to Example 1, Step 4, by substituting glycine benzyl ester hydrochloride for 2-benzyloxy-ethylamine hydrochloride, the title compound was obtained as a white powder; ES-MS 690 (m + 1).

EXAMPLE 4

N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-(4-phenylbutyl)-N^2-[[4-(phenylmethoxy)phenyl]methyl]glycinamide

According to Example 1, Step 4, by substituting 4-phenybutylamine for 2-benzyloxyethylamine hydrochloride and omitting Et_3N, the title compound was obtained as a white foam, mp 58-61°C; ES-MS 674 (m + 1).

EXAMPLE 5

N-[N-[N-[(Phenylmethoxy)carbonyl]-L-histidyl]-N-[[4-(phenylmethoxy)phenyl]methyl]glycyl]glycine methyl ester

According to Example 1, Step 4, by substituting glycine methyl ester hydrochloride for 2-benzyloxyethylamine, the title compound was obtained as a white foam; ES-MS 614 (m + 1).

EXAMPLE 6

N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-[[4-(phenylmethoxy)phenyl]methyl]glycyl-N-phenylmethylglycinamide

According to Example 1, Step 4, by substituting N-phenylmethylglycinamide trifluoroacetic acid salt for 2-benzyloxyethylamine hydrochloride, the title compound was obtained as a white powder; ES-MS 689 (m + 1).

EXAMPLE 7

N-[N-[N-[(Phenylmethoxy)carbonyl]-L-histidyl]-N-[[4-(phenylmethoxy)phenyl]methyl]glycyl]-ß-alanine phenylmethyl ester

According to Example 1, Step 4, by substituting β-alanine benzyl ester hydrochloride for 2-benzyloxyethylamine hydrochloride, the title compound was obtained as a white foam; ES-MS 704 (m + 1).

EXAMPLE 8

N-[N-[(4-Methoxyphenyl)methyl]-N-[N-[(phenylmethoxy)-carbonyl]-L-histidyl]glycyl]glycine phenylmethyl ester

Step 1: N-(4-Methoxybenzylamino)acetic acid ethyl ester

To a mixture of glycine ethyl ester hydrochloride (1.03 g, 7.38 mmol) and 4-methoxybenzaldehyde (0.71 g, 5.21 mmol) in CH_2Cl_2 (25 mL) was added KOAc (0.51 g, 5.21 mmol) followed by sodium triacetoxyborohydride (1.44 g, 6.78 mmol). The mixture was stirred at room temperature for 4 hours. Aqueous $NaHCO_3$ was added and the mixture was stirred for 30 minutes. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (60% EtOAc/hexane) gave 1.0 g (86%) of the title compound as a colorless oil; CI-MS 224 (m + 1).

Step 2: N-[(4-Methoxyphenyl)methyl]-N-[N-[(phenyl-methoxy)carbonyl]-L-histidyl]glycine ethyl ester

According to Example 1, Step 2, by substituting the compound from Step 1 above for N-[[4-(phenyl-methoxy)phenyl]methyl]glycine methyl ester, the title compound was obtained as a white foam; ES-MS 495 (m + 1).

Step 3: N-[(4-Methoxyphenyl)methyl]-N-[N-[(phenyl-methoxy)carbonyl]-L-histidyl]glycine

According to Example 1, Step 3, but substituting the compound from Step 2 above for N-[N-[(phenyl-methoxy)carbonyl]-L-histidyl]-N-[[4-(phenylmethoxy)-phenyl]methyl]glycine methyl ester, the title compound was obtained as a white solid.

Step 4: N-[(4-Methoxyphenyl)methyl]-N-[N-[(phenylmethoxy)carbonyl]-L-histidyl]glycine phenylmethyl ester

To a solution of the acid from Step 3 (0.41 g, 0.88 mmol) in DMF (5 mL) was added HOBT hydrate (0.16 g, 1.05 mmol) and DCC (0.22 g, 1.05 mmol) followed by glycine benzyl ester hydrochloride (0.18 g, 0.88 mmol). Et_3N (0.12 mL, 0.88 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was filtered, the filtrate was diluted with $CHCl_3$, washed twice with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Flash chromatography (2-5% MeOH/$CHCl_3$) gave 0.29 g (54%) of the title compound as a white foam; ES-MS 614 (m + 1).

EXAMPLE 9

N-[(4-Methoxyphenyl)methyl]-N-[N-[(phenylmethoxy)-carbonyl]-L-histidyl]glycine phenylmethyl ester

According to Example 8, Step 4, by substituting benzyl alcohol for glycine benzyl ester hydrochloride and omitting Et_3N, the title compound was obtained as a white foam; ES-MS 557 (m + 1).

EXAMPLE 10

N-[(Phenylmethoxy)carbonyl]-D-histidyl-N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide

Step 1: N-BOC-N-[2-(phenylmethoxy)ethyl]glycinamide

To a solution of BOC-glycine (0.47 g, 2.69 mmol) in EtOAc (10 mL) was added HOBT hydrate (0.49 g, 3.22 mmol) followed by DCC (0.66 g, 3.22 mmol). After 30 minutes, a solution of benzyloxyethylamine (0.41 g, 2.69 mmol) in EtOAc (5 mL) was added and the mixture was stirred overnight at room temperature. The mixture was filtered, and the filtrate was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, brine, dried over

$MgSO_4$, and concentrated. Flash chromatography (EtOAc) gave 0.72 g (87%) of the title compound as a light yellow oil which slowly solidified; CI-MS 309 (m + 1). Anal. calcd. for $C_{16}H_{24}N_2O_4$:

C, 62.32; H, 7.84, N, 9.08.

Found: C, 61.94; H, 7.83; N, 9.12.

Step 2: N-[2-Phenylmethoxy)ethyl]glycinamide trifluoroacetic acid salt

To a solution of the compound from Step 1 above (0.67 g, 2.17 mmol) in CH_2Cl_2 (10 mL) was added TFA (1 mL). The solution was stirred at room temperature for 4 hours and then concentrated. The residue was twice taken up in CH_2Cl_2 and reconcentrated. Obtained 0.78 g of a light yellow gum which was used in Step 3 without further purification; CI-MS 209 (m + 1).

Step 3: N-[2-(Phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]glycinamide

To a solution of the compound from Step 2 above (0.69 g, 2.14 mmol) in CH_2Cl_2 (10 mL) at 0°C was added 4-benzyloxybenzaldehyde (0.45 g, 2.14 mmol) followed by sodium triacetoxyborohydride (0.59 g, 2.78 mmol). The mixture was allowed to warm to room temperature and stirred for six hours. Saturated aqueous $NaHCO_3$ was added and the mixture was stirred for 30 minutes. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (2-5% MeOH/$CHCl_3$) gave 0.46 g (53%) of the title compound as a colorless oil; CI-MS 405 (m + 1).

Step 4: N-[(Phenylmethoxy)carbonyl]-D-histidyl-N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]-methyl]glycinamide

To a suspension of CBZ-D-histidine (0.093 g, 0.32 mmol) in DMF (2 mL) was added HOBT hydrate (0.059 g, 0.39 mmol) followed by DCC (0.080 g, 0.39 mmol). A solution of the compound from Step 3 above (0.13 g, 0.32 mmol) in DMF (2 mL) was added and the mixture was stirred overnight at room temperature. The mixture was filtered, and the filtrate was diluted with $CHCl_3$, washed twice with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Flash chromatography (2-5% MeOH/$CHCl_3$) gave 0.10 g (45%) of the title compound as a white powder; ES-MS 676 (m + 1).

Anal. calcd. for $C_{39}H_{41}N_5O_6 \cdot 0.5H_2O$:
C, 68.39; H, 6.18; N, 10.22.
Found: C, 68.56; H, 6.28; N, 9.83.

EXAMPLE 11

N-[(Phenylmethoxy)carbonyl]-L-histidyl-N^2-[(1,1'-biphenyl)-4-ylmethyl]-N-[2-(phenylmethoxy)ethyl]-glycinamide

Step 1: N^2-[(1,1'-Biphenyl)-4-ylmethyl]-N-[2-phenylmethoxy)ethyl]glycinamide

According to Example 10, Step 3, by substituting 4-biphenylcarboxaldehyde for 4-benzyloxybenzaldehyde, the title compound was obtained as a colorless oil which slowly solidified;
^1H NMR (300 MHz, $CDCl_3$): ∂ 7.65-7.27 (m, 15H), 4.55 (s, 2H), 3.82 (s, 2H), 3.62-3.50 (m, 4H), 3.35 (s, 2H).

Step 2: N-[(Phenylmethoxy)carbonyl]-L-histidyl-N^2-[(1,1'-biphenyl)-4-ylmethyl]-N-[2-(phenylmethoxy)-ethyl]glycinamide

According to Example 10, Step 4, by substituting the compound from Step 1 above for N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide and CBZ-histidine for CBZ-D-histidine, the title compound was obtained as a white foam; ES-MS 646 (m + 1).

EXAMPLE 12

N-[(Phenylmethoxy)carbonyl]-L-histidyl-N^2-[4-(phenylmethoxy)butyl]-N-[2-(phenylmethoxy)ethyl]glycinamide

Step 1: N^2-[4-(Phenylmethoxy)butyl]-N-[2-(phenylmethoxy)ethyl]glycinamide

According to Example 10, Step 3, by substituting 4-benzyloxybutyraldehyde for 4-benzyloxybenzaldehyde, the title compound was obtained as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (br m, 1H), 7.38-7.25 (m, 10H), 4.53 (s, 2H), 4.50 (s, 2H), 3.60-3.42 (m, 6H), 3.25 (s, 2H), 2.61 (m, 2H), 1.71-1.50 (m, 5H).

Step 2: N-[(Phenylmethoxy)carbonyl]-L-histidyl-N^2-[4-(phenylmethoxy)butyl]-N-[2-(phenylmethoxy)ethyl]-glycinamide

According to Example 10, Step 4, by substituting the compound from Step 1 above for N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide and CBZ-histidine for CBZ-D-histidine, the title compound was obtained as a white foam; ES-MS 642 (m + 1).

EXAMPLE 13

N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-(3-phenoxypropyl)-N^2-[[4-(phenylmethoxy)phenyl]methyl]glycinamide

Step 1: N-(3-Phenoxypropyl)-N^2-[[4-(phenylmethoxy)-phenyl]methyl]glycinamide

According to Example 10, Step 3, by substituting N-(3-phenoxypropyl)glycinamide hydrochloride for N-[2-(phenylmethoxy)ethyl]glycinamide trifluoroacetic acid salt, the title compound was obtained as a colorless oil which slowly solidified, mp 55-56°C; CI-MS 405 (m + 1).

Step 2: N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-(3-phenoxypropyl)-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide

According to Example 10, Step 4, by substituting the compound from Step 1 above for N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide and CBZ-histidine for CBZ-D-histidine, the title compound was obtained as a white foam; ES-MS 676 (m + 1).

EXAMPLE 14

N-[N-[N-[(Phenylmethoxy)carbonyl]-L-histidyl]-N-[[3-(phenylmethoxy)phenyl]methyl]glycyl]glycinephenylmethyl ester

Step 1: N-BOC-glycylglycine benzyl ester

According to Example 10, Step 1, by substituting glycine benzyl ester hydrochoride for benzyloxyethylamine and adding 1 eq. of Et_3N, the title compound was obtained as a colorless oil; CI-MS 323 (m + 1).

Step 2: Glycylglycine benzyl ester trifluoroacetic acid salt

According to Example 10, Step 2, by substituting the compound from Step 1 above for N-BOC-N-[2-(phenylmethoxy)ethyl]glycinamide, the title compound was obtained as a white solid; CI-MS 223 (m + 1).

Anal. calcd. for $C_{11}H_{14}N_2O_3 \cdot CF_3CO_2H$:
C, 46.43; H, 4.61; N, 8.33.
Found: C, 46.43; H, 4.50; N, 8.33.

Step 3: N-[2-(Phenylmethoxy)ethyl]-N-[[3-(phenylmethoxy)phenyl]methyl]glycine benzyl ester

According to Example 10, Step 3, by substituting 3-benzyloxybenzaldehyde for 4-benzyloxybenzaldehyde and the compound from Step 2 above for N-[2-phenylmethoxy)-ethyl]glycinamide trifluoroacetic acid salt, the title compound was obtained as a colorless oil;
^1H NMR (300 MHz, $CDCl_3$): ∂ 7.74 (br m, 1H), 7.48-7.21 (m, 11H), 6.98 (s, 1H), 6.91 (m, 2H), 5.20 (s, 2H), 5.09 (s, 2H), 4.13 (d, J = 6 Hz, 2H), 3.78 (s, 2H), 3.36 (s, 2H).

Step 4: N-[N-[N-[(Phenylmethoxy)carbonyl]-L-histidyl]-N-[[3-(phenylmethoxy)phenyl]methyl]glycyl]glycine-phenylmethyl ester

According to Example 10, Step 4, by substituting the compound from Step 3 above for N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide and CBZ-histidine for CBZ-D-histidine, the title compound was obtained as a white foam; ES-MS 690 (m + 1).

EXAMPLE 15

(S)-[1-(1H-Imidazol-3-ylmethyl)-2-oxo-2-[[2-(phenylmethoxy)ethyl][4-(phenylmethoxy)phenyl]methyl]amino]-ethyl]carbamic acid, phenylmethyl ester

Step 1: [[2-(Phenylmethoxy)ethyl][4-(phenylmethoxy)-phenyl]methyl]amine

To a solution of benzyloxyethylamine (0.75 g, 4.96 mmol) in CH_2Cl_2 (20 mL) at 0°C was added 4-benzyloxybenzaldehyde (0.96 g, 4.51 mmol). Sodium triacetoxyborohydride (1.24 g, 5.86 mmol) was added followed by AcOH (0.26 mL, 4.51 mmol). The mixture was allowed to warm to room temperature and stirred for 4 hours. Saturated aqueous $NaHCO_3$ was added and the mixture was stirred for 30 minutes. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (2% MeOH/$CHCl_3$) gave 1.04 g (66%) of the title compound as a colorless oil; CI-MS 348 (m + 1).

Step 2: (S)-[1-(1H-Imidazol-3-ylmethyl)-2-oxo-2-[[2-(phenylmethoxy)ethyl][4-(phenylmethoxy)phenyl]methyl]-aminolethyl]carbamic acid, phenylmethyl ester

According to Example 10, Step 4, by substituting the compound from Step 1 above for N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide and CBZ-histidine for CBZ-D-histidine, the title compound was obtained as a white foam; ES-MS 619 (m + 1).

Anal. calcd. for $C_{37}H_{38}N_4O_5$:
C, 71.83; H, 6.19; N, 9.05.
Found: C, 71.44; H, 6.19; N, 8.99.

EXAMPLE 16

(S)-[1-(1H-imidazol-3-ylmethyl)-2-oxo-2-[bis[[4-(phenylmethoxy)phenyl]methyl]amino]ethyl]carbamic acid, phenylmethyl ester

Step 1: Bis[[4-(phenylmethoxy)phenyl]methyl]amine

According to Example 8, Step 1, by substituting 4-benzyloxybenzylamine hydrochloride for glycine ethyl ester hydrochloride and 4-benzyloxybenzaldehyde for 4-methoxybenzaldehyde, the title compound was obtained as a white solid; CI-MS 410 (m + 1).

Step 2: (S)-[1-(1H-imidazol-3-ylmethyl)-2-oxo-2-[bis-[[4-(phenylmethoxy)phenyl]methyl]amino]ethyl]carbamic acid, phenylmethyl ester

According to Example 10, Step 4, by substituting the compound from Step 1 above for N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide and CBZ-histidine for CBZ-D-histidine, the title compound was obtained as a white foam; ES-MS 681 (m + 1).

Anal. calcd. for $C_{42}H_{40}N_4O_5$:

C, 74.10; H, 5.92; N, 8.23.

Found: C, 73.87; H, 6.00; N, 8.15.

EXAMPLE 17

O-(Phenylmethyl)-N-[1,2,3,4-tetrahydro-2-[N-[(phenylmethoxy)carbonyl]-L-histidyl]-7-(phenylmethoxy)-L-3-isoquinolinecarbonyl]-L-serine methyl ester

Step 1: N-[N-BOC-[1,2,3,4-tetrahydro-7-(phenylmethoxy)-L-3-isoquinolinecarbonyl]]-L-serine methyl ester

To a solution of N-BOC-7-(phenylmethoxy)-L-3-isoquinoline carboxylic acid (0.50 g, 1.30 mmol) in EtOAc (10 mL) was added HOBT (0.24 g, 1.56 mmol)

followed by DCC (0.32 g, 1.56 mmol). Serine methyl ester hydrochloride (0.32 g, 1.30 mmol) was added followed by Et_3N (0.22 mL, 1.56 mmol) and the mixture was stirred overnight at room temperature. The mixture was filtered, and the filtrate was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. Flash chromatography (40% EtOAc/hexane) gave 0.67 g (89%) of the title compound as a sticky foam; CI-MS 575 (m + 1).

Anal. calcd. for $C_{33}H_{38}N_2O_7$:

C, 68.97; H, 6.67; N, 4.87.

Found: C, 68.57; H, 6.79; N, 4.99.

Step 2: N-[1,2,3,4-tetrahydro-7-(phenylmethoxy)-L-3-isoquinolinecarbonyl]-L-serine methyl ester trifluoroacetic acid salt

According to Example 10, Step 2, by substituting the compound from Step 1 above for N-BOC-N-[2-(phenylmethoxy)ethyl]glycinamide, the title compound was obtained as a white solid; CI-MS 475 (m + 1).

Step 3: O-(Phenylmethyl)-N-[1,2,3,4-tetrahydro-2-[N-[(phenylmethoxy)carbonyl]-L-histidyl]-7-(phenylmethoxy)-L-3-isoquinolinecarbonyl]-L-serine methyl ester

According to Example 10, Step 4, by substituting the compound from Step 2 above for N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide and CBZ-histidine for CBZ-D-histidine, the title compound was obtained as a white solid, mp 82-88°C; ES-MS 746 (m + 1).

EXAMPLE 18

[1-(1H-imidazol-4-ylmethyl)-2-oxo-2-[1,2,3,4-tetrahydro-7-(phenylmethoxy)-3-[[2-(phenylmethoxy)ethyl]aminol carbonyl]-2-isoquinolinyl]ethyl]carbamic acid, phenylmethyl ester

Step 1: N-[BOC-1,2,3,4-tetrahydro-7-(phenylmethoxy)-L-3-isoquinolinyl]-N'-[2-(phenylmethoxy)ethyl]-carboxamide

According to Example 17, Step 1, by substituting benzyloxyethylamine for serine methyl ester hydrochloride and omitting Et_3N, the title compound was obtained as a colorless oil; CI-MS 517 (m + 1).

Step 2: N-[1,2,3,4-tetrahydro-7-(phenylmethoxy)-L-3-isoquinolinyl]-N'-[2-(phenylmethoxy)ethyl]carboxamide

According to Example 17, Step 2, by substituting the compound from Step 1 above for N-[1,2,3,4-tetrahydro-7-(phenylmethoxy)-L-3-isoquinolinecarbonyl]-L-serine methyl ester trifluoroacetic acid salt, the title compound was obtained as a light yellow oil; CI-MS 417 (m + 1).

Step 3: [1-(1H-imidazol-4-ylmethyl)-2-oxo-2-[1,2,3,4-tetrahydro-7-(phenylmethoxy)-3-[[2-(phenylmethoxy)ethyl]aminol carbonyl]-2-isoquinolinyl]ethyl]-carbamic acid, phenylmethyl ester

According to Example 10, Step 4, by substituting the compound from Step 2 above for N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]-glycinamide, the title compound was obtained as a mixture of separable diastereomers; Diastereomer A: ES-MS 688 (m + 1); Diastereomer B: ES-MS 688 (m + 1).

EXAMPLE 19

1-(2-Methoxy-2-oxoethyl)-N-[(phenylmethoxy)carbonyl]-L-histidyl-N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]glycinamide

To a solution of N-[(phenylmethoxy)carbonyl]-L-histidyl-N-[2-(phenylmethoxy)ethyl]-N'-[[4-(phenylmethoxy)phenyl]methyl]glycinamide (Example 1) (1.00 g, 1.48 mmol) in CH_2Cl_2 (10 mL) was added $(iPr)_2NEt$ (0.28 mL, 1.63 mmol) followed by methyl bromoacetate (0.14 mL, 1.48 mmol). The solution was stirred for two days at room temperature. After concentration and flash chromatography (1-2% MeOH/$CHCl_3$), 0.91 g (82%) of the title compound was obtained as a white foam; ES-MS 748 (m + 1).

Anal. calcd. for $C_{42}H_{45}N_5O_8$:
C, 67.46; H, 6.07; N, 9.36.
Found: C, 67.09; H, 5.91; N, 9.12.

EXAMPLE 20

1-(Carboxymethyl)-N-[(phenylmethoxy)carbonyl]-L-histidyl-N^2-[[4-(phenoxymethyl)phenyl]methyl]-N-[2-(phenylmethoxy)ethyl]glycinamide

According to Example 1, Step 3, by substituting the compound from Example 19 for N-[N-[(phenylmethoxy)-carbonyl]-L-histidyl]-N-[[4-(phenylmethoxy)phenyl]methyl]glycine methyl ester, the title compound was obtained as a white powder; ES-MS 734 (m + 1), 740 (m + Li).

EXAMPLE 21

Solid phase supported N-[N-(9H-Fluoren-9-ylmethoxy)-carbonyl-histidyl] methyl ester {Fmoc-D-His-(2-Cl-Tr Resin)-CO_2Me}

To a suspension of Fmoc-His-CO_2Me (1.0 mmol) in CCl_3H (10 mL) was added 2-chlorotrityl chloride resin (Novabiochem) (1.0 g) followed by DIEA (1.1 mmol). The resulting mixture was subjected to brief sonication to

disperse the resin and then agitated on a shaker for 2.5 hours. The modified resin was collected by filtration, washed with $CHCl_3$ (5 x 10 mL) and dried in vacuo for 18 hours to yield the loaded resin.

EXAMPLE 22

Methyl {(4-Benzyloxy-benzyl)-[2-(3-benzyl-ureido)-3-(3H-imidazol-4-yl)propionyl]amino}acetic acid ester

Fmoc-His(2-Cl-Tr-resin)-CO_2Me (from Example 21 above, 0.15 mmol) was suspended in 20% piperidine in DMF (v/v, 4 mL). The resulting suspension was subjected to sonication for 10 minutes and then agitated by shaking for 30 minutes. The resin was filtered and washed with DMF three times. The resin was again subjected to the same reaction conditions for an additional 20 minutes. The resin was filtered and washed with DMF four times, $CHCl_3$ three times to provide His(2-Cl-Tr-resin)-CO_2Me which was suspended in DCM (10 mL), agitated for 10 minutes by shaking, treated with benzyl isocyanate (0.6 mmol) and agitated an additional 30 minutes. The resin was filtered, washed with DCM three times, resuspended in DCM and the benzyl isocyanate treatment was repeated. The resin was filtered and washed with DMF two times, and $CHCl_3$ five times to give BnNHCO-His(2-Cl-Tr-resin)-CO_2Me which was next suspended in a 3:1 mixture of dioxane/MeOH (3 mL) and treated with aqueous 1.0N NaOH (0.6 mmol). The suspension was agitated by shaking for 18 hours, filtered, washed sequentially with a 2:1 mixture of dioxane and 10% aqueous citric acid (3 x 10 mL), dioxane/MeOH (3 x 10 mL) and $CHCl_3$ (3 x 10 mL) to provide BnNHCO-His(2-Cl-Tr-resin)-CO_2H. The BnNHCO-His(2-Cl-Tr-resin)-CO_2H was suspended in DMF (4 mL) and treated with a carbodiimide coupling reagent such as DIC (0.6 mmol) and HOBT (0.6 mmol). The resulting mixture was stirred 30 minutes and

(4-benzyloxybenzylamino)acetic acid methyl ester (0.6 mmol) was added. The resulting mixture was shaken 18 hours before filtering the resin and washing with DMF three times and $CHCl_3$ three times. The resin was suspended in DMF (10 mL) and the carbodiimide/BT/ 4-benzyloxybenzylamino acetic acid methyl ester coupling reaction was repeated. After 18 hours the resin was filtered and washed with 10 mL each of MeOH two times, DCM three times, DMF two times, MeOH two times, and $CHCl_3$ two times to give BnNHCO-His(2-Cl-Tr-resin)-$CON(CH_2CO_2Me)CH_2$-(4-BnO-Ph). The substituted dipeptide was cleaved from the resin by treatment with 70% TFA in DCM, shaking for 1 hour at room temperature. The supernate containing the free dipeptide was filtered away from the resin and the resin washed with DCM three times. The combined supernate and washings were concentrated in vacuo to provide BnNHCO-His-$CON(CH_2CO_2Me)CH_2$-(4-BnO-Ph)·TFA. The product was partitioned between water and DCM and both layers were treated dropwise with saturated aqueous $NaHCO_3$ until the aqueous layer remained basic. The layers were separated and the organic phase was washed with saturated aqueous NaCl and dried ($MgSO_4$). Filtration and concentration yielded BnNHCO-His-$CON(CH_2CO_2Me)CH_2$-(4-BnO-Ph).

EXAMPLE 23

Multiple, Simultaneous Solid Phase Synthesis

The method described in Example 22 may be employed in simultaneous multiple syntheses using the apparatus described by DeWitt S.H., et al., Proc. Natl. Acad. Sci. USA, 90:6909 (1993). Fmoc-His(2-Cl-tr-resin)-CO_2Me prepared according to Example 21 (100-200 mg) is placed in each of 40 gas dispersion tubes and the tubes are placed in the multiple synthesis apparatus. The sequential deprotection and coupling reactions

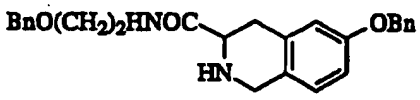
described in Example 22 are followed, employing the following acylating agents and amines in all possible combinations:

Acylating agents

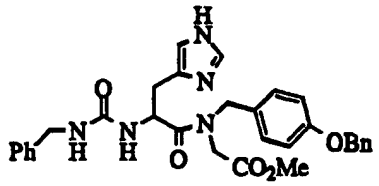
1) benzyl isocyanate
2) benzyloxycarbonyl NHOS ester
3) phenyl isocyanate
4) 3-pyridylmethyl isocyanate
5) phenethyl isocyanate
6) butyl isocyanate
7) phenylacetyl chloride
8) 1-naphthyl isocyanate

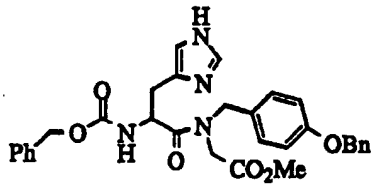
Amines

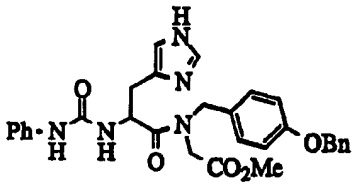
1) $HN(CH_2CO_2Me)CH_2(4\text{-}BnO\text{-}Ph)$
2) $HN(CH_2CONHCH_2CH_2OBn)CH_2(4\text{-}BnO\text{-}Ph)$
3) $HN(CH_2CONHCH_2CH_2SBn)CH_2(4\text{-}BnO\text{-}Ph)$
4) $HN(CH_2CONHCH_2CH_2OBn)CH_2(4\text{-}EtO\text{-}Ph)$

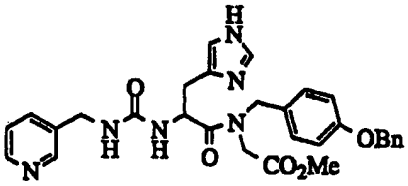
5) 

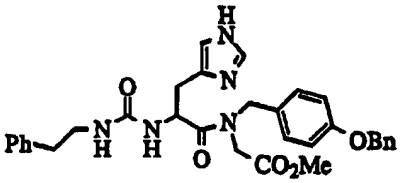
Following cleavage from the resin and work-up as described in Example 22, the following 40 substituted analogs of Formula I are isolated:

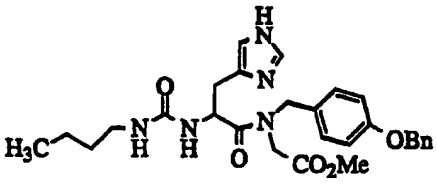
1. 

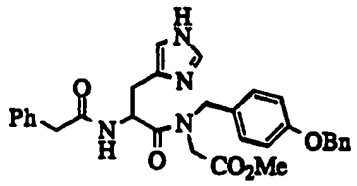
2. 

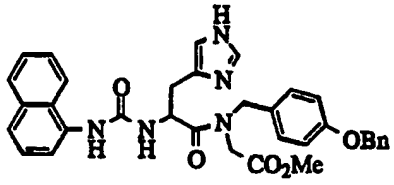
3. 

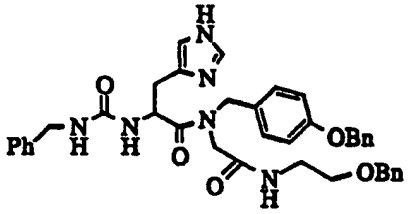
4. 

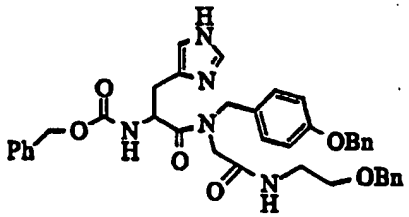
5. 

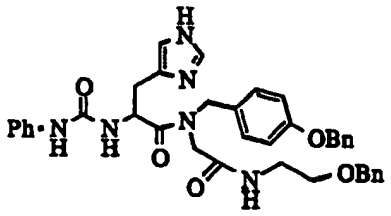
6. 

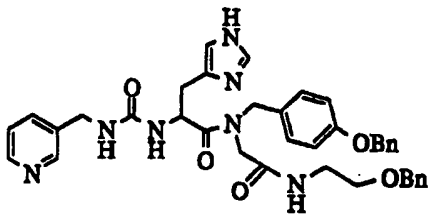
7. 

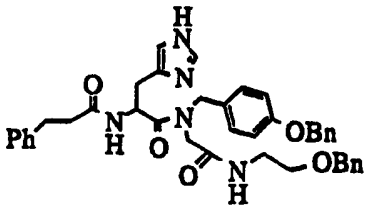
8. 

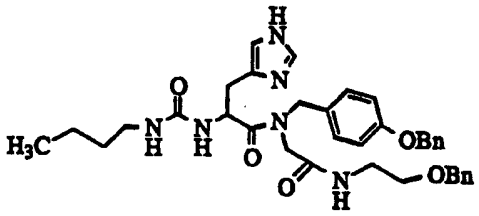
9. 

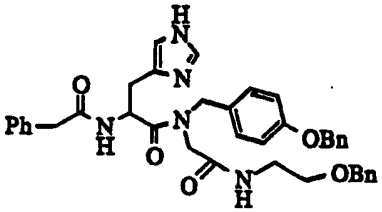
10. 

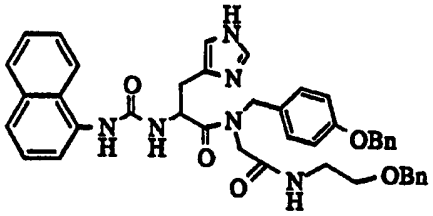
11. 

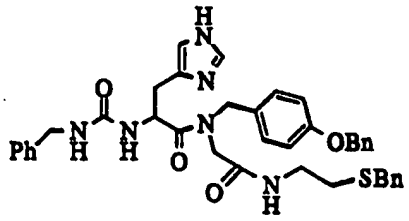
12. 

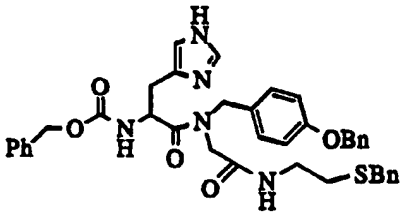
13. 

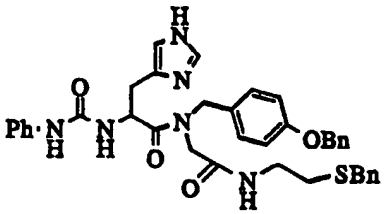
14. 

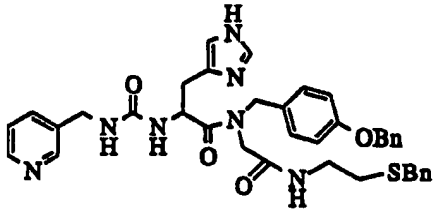
15. 

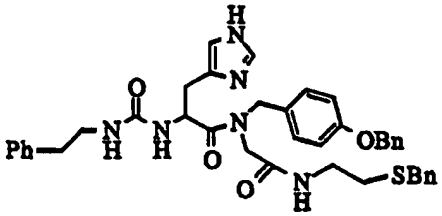
16. 

17. 

18. 

19. 

20. 

21. 

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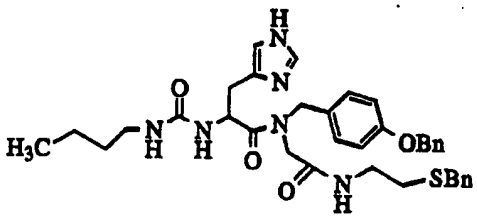

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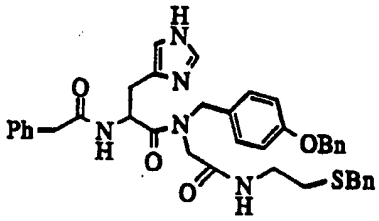

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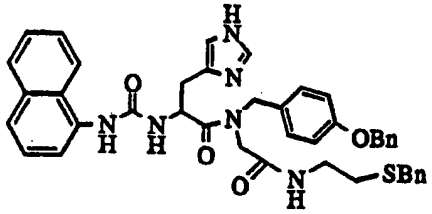

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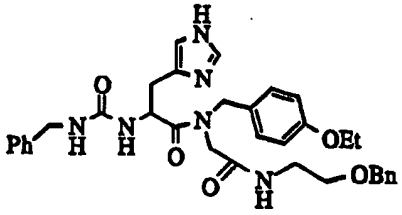

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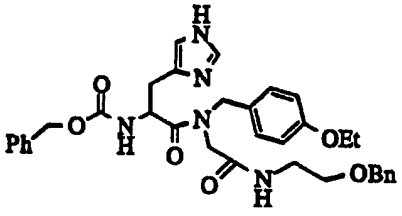

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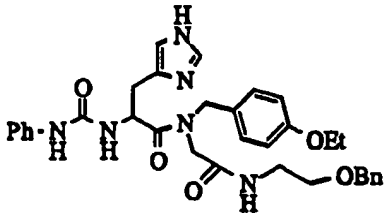

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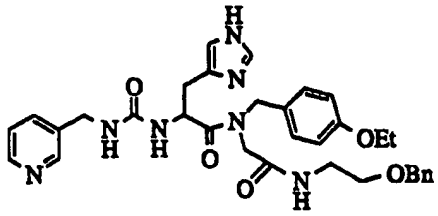

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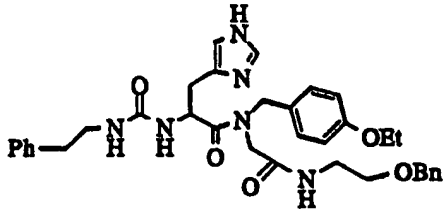

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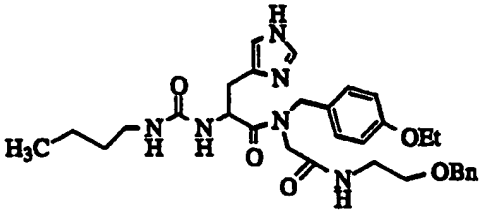

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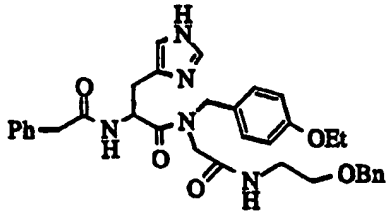
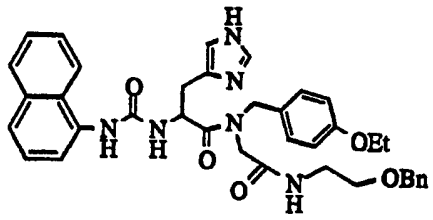
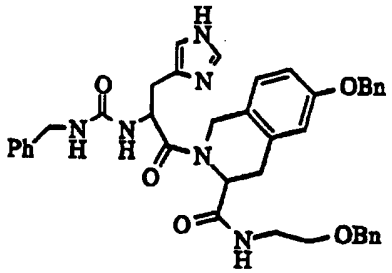
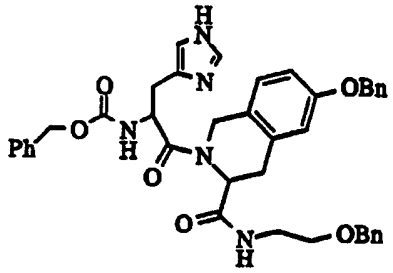
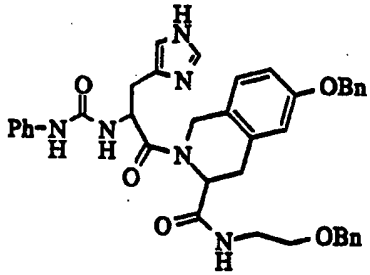


32. 

33. 

34. 

35. 

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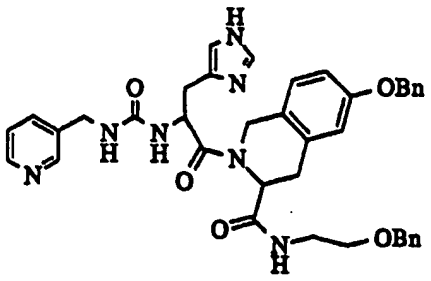
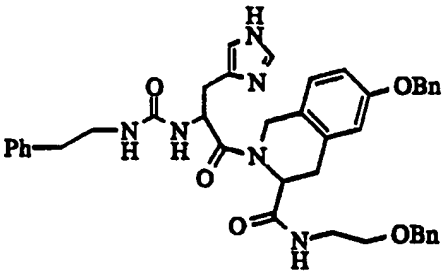
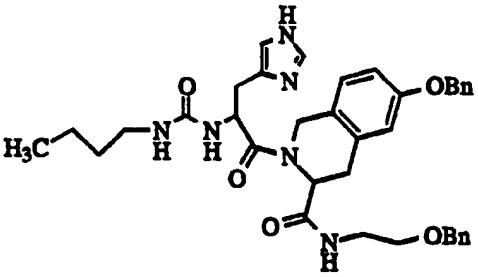
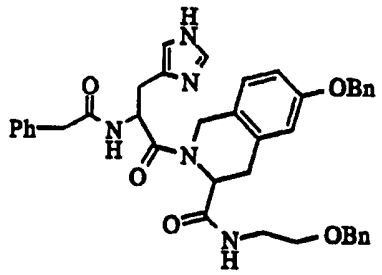


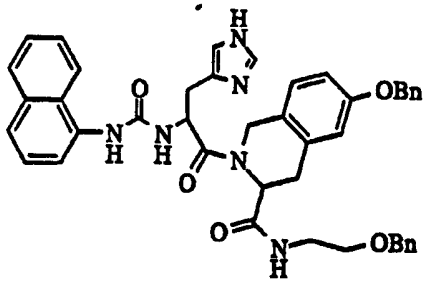
37.



38.



39. 

40. 

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Hodges, John C.
Bolton, Gary L.
Wilson, Michael W.

(ii) TITLE OF INVENTION: Histidine and Homohistidine Derivatives as Inhibitors of Protein Farnesyltranferase

(iii) NUMBER OF SEQUENCES: 4

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Warner-Lambert Company
(B) STREET: 2800 Plymouth Rd
(C) CITY: Ann Arbor
(D) STATE: MI
(E) COUNTRY: US
(F) ZIP: 48105

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: Patent In Release #1.0, Ver #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: US
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Ashbrook, Charles W.

(B) REGISTRATION NUMBER: 27,610

(C) REFERENCE/DOCKET NUMBER: PD-5077

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 313 996-5215

(B) TELEFAX: 313 996-1553

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Cys Xaa Xaa Xaa
1

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Cys Xaa Xaa Xaa
1

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Cys Xaa Xaa Xaa
1

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

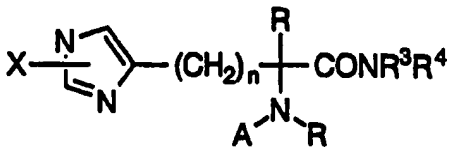
(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Cys Xaa Xaa Xaa
1

CLAIMS

1. An inhibitor of protein farnesyltransferase which is a histidine or homohistidine derivative of the Formula I,



I

wherein:

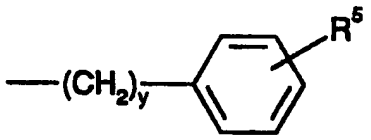
n = 1 or 2;

A = COR^2, CO_2R^2, $CONHR^2$, CSR^2, $C(S)OR^2$, $C(S)NHR^2$, or SO_2R^2 with R^2 as defined below;

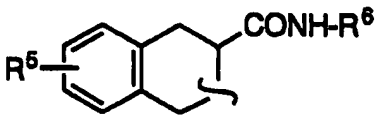
R = independently H or Me;

R^2 = alkyl, $(CH_2)_m$-cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heteroaryl with m = 0, 1, 2, or 3;

R^3 and R^4 = independently



or $(CH_2)_nCONH\text{-}R^6$ with y = 1-5 and n as defined above and with R^5 and R^6 as defined below, or R^3 and R^4 are connected together to form a ring of the following type:



with R^5 and R^6 as defined below, or $(CH_2)_x\text{-}R^7$, with x = 2-5, and R^7 as defined below;

R^5 = R^2, OR^2, or SR^2 with R^2 as defined above;

R^6 = $(CH_2)_nR^5$, $(CH_2)_nCO_2R^2$, $(CH_2)_nCONHR^2$, $(CH_2)_nCONH(CH_2)_{n+1}R^5$, $CH(COR^8)(CH_2)_nR^5$, with n, R^2, and R^5 as defined above and R^8 as defined below;

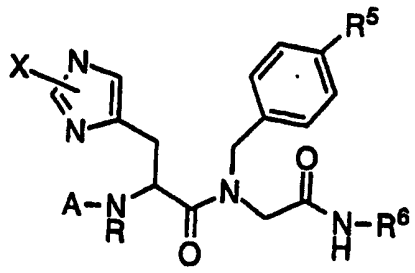
R^7 = $(CH_2)_m$-cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heteroaryl, $O(CH_2)_m$-cycloalkyl, $O(CH_2)_m$-aryl, $O(CH_2)_m$-heteroaryl with m = 0, 1, 2, or 3;

R^8 = OH, O-alkyl, NH_2, or NH-alkyl; and

X = H, Me, $(CH_2)_nCO_2R^9$, or $(CH_2)_nP(O)(OR^9)_2$, with R^9 = H or alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 which is a compound of Formula II:



II

wherein:

A is limited to CO_2R^2, $CONHR^2$, $C(S)OR^2$, or $C(S)NHR^2$ with R^2 as defined below;

R = H or Me;

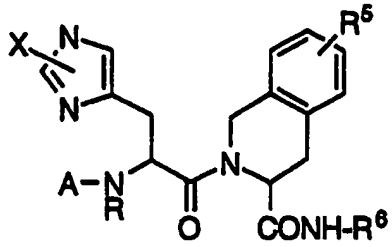
R^2 is limited to alkyl, $(CH_2)_m$-cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heteroaryl, with m = 0, 1, 2, or 3;

R^5 is limited to $(CH_2)_m$-aryl, O-$(CH_2)_m$-aryl, or O-$(CH_2)_m$-heteroaryl with m as defined above;

R^6 is limited to CH_2-R^5, $CH_2CO_2R^2$, CH_2CONHR^2, with n = 1 or 2, and with R^5 and R^2 as defined above; and

X is limited to H or Me;
or a pharmaceutically acceptable salt thereof.

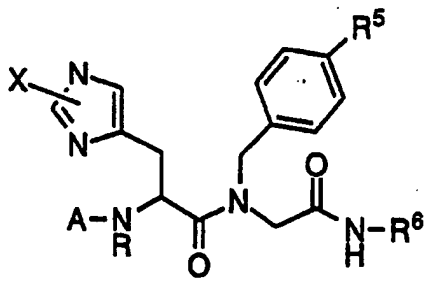
3. A compound according to Claim 1 which is a compound of Formula III:



III

wherein:
A is limited to CO_2R^2, $CONHR^2$, $C(S)OR^2$, or $C(S)NHR^2$ with R^2 as defined below;
R = H or Me;
R^2 is limited to alkyl, $(CH_2)_m$-cycloalkyl, $(CH_2)_m$-aryl, $(CH_2)_m$-heteroaryl, with m = 0, 1, 2, or 3;
R^5 is limited to $(CH_2)_m$-aryl, O-$(CH_2)_m$-aryl, or O-$(CH_2)_m$-heteroaryl with m as defined above;
R^6 is limited to CH_2-R^5, $CH_2CO_2R^2$, CH_2CONHR^2, with n = 1 or 2, and with R^5 and R^2 as defined above; and
X is limited to H or Me;
or a pharmaceutically acceptable salt thereof.

4. A compound according to Claim 1 which is a compound of Formula II:



II

wherein:

A is further limited to CO_2R^2 or $CONHR^2$, with R^2 as defined below;

R is limited to H;

R^2 is further limited to alkyl, or $(CH_2)_m$-aryl with m = 0, 1, 2, or 3;

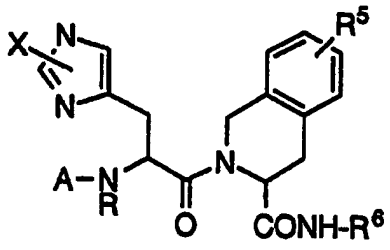
R^5 is further limited to $(CH_2)_m$-aryl or O-$(CH_2)_m$-aryl with m as defined above;

R^6 is limited to CH_2-R^5 or CH_2CONHR^2, with n = 1 or 2, and with R^5 and R^2 as defined above; and

X is limited to H or Me;

or a pharmaceutically acceptable salt thereof.

5. A compound according to Claim 1 which is a compound of Formula III:



III

wherein:

A is further limited to CO_2R^2 or $CONHR^2$, with R^2 as defined below;

R is limited to H;

R^2 is further limited to alkyl, or $(CH_2)_m$-aryl with m = 0, 1, 2, or 3;

R^5 is further limited to $(CH_2)_m$-aryl or O-$(CH_2)_m$-aryl with m as defined above;

R^6 is limited to CH_2-R^5 or CH_2CONHR^2, with n = 1 or 2, and with R^5 and R^2 as defined above; and

X is limited to H or Me;

or a pharmaceutically acceptable salt thereof.

6. A compound of Claim 1 which is:
N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-[2-(phenylmethoxy)ethyl]-N^2-[[4-(phenylmethoxy)phenyl]methyl]glycinamide.

7. A compound of Claim 1 which is:
N-[(Phenylmethoxy)carbonyl]-L-histidyl-N^2-[(1,1'-biphenyl)-4-ylmethyl]-N-[2-(phenylmethoxy)ethyl]glycinamide.

8. A compound of Claim 1 which is:
N-[N-[N-[(Phenylmethoxy)carbonyl]-L-histidyl]-N-[[4-(phenylmethoxy)phenyl]methyl]glycyl]-glycine phenylmethyl ester.

9. A compound of Claim 1 which is:
N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-(4-phenylbutyl)-N^2-[[4-(phenylmethoxy)-phenyl]methyl]glycinamide.

10. A compound of Claim 1 which is:
N-[(Phenylmethoxy)carbonyl]-L-histidyl-N-(3-phenoxypropyl)-N^2-[[4-(phenylmethoxy)-phenyl]methyl]glycinamide.

11. A compound of Claim 1 which is:
(S)-[1-(1H-Imidazol-3-ylmethyl)-2-oxo-2-[[2-(phenylmethoxy)ethyl][4-(phenylmethoxy)-phenyl]methyl]amino]ethyl]carbamic acid, phenylmethyl ester.

12. A compound of Claim 1 which is:
[1-(1H-Imidazol-4-ylmethyl)-2-oxo-2-[1,2,3,4-tetrahydro-7-(phenylmethoxy)-3-[[2-(phenylmethoxy)ethyl]amino]carbonyl]-2-isoquinolinyl]ethyl]carbamic acid, phenylmethyl ester.

13. A method of treating tissue proliferative diseases comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

14. A pharmaceutical composition adapted for administration as an antiproliferative agent comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

15. A method of treating cancer comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

16. A pharmaceutical composition adapted for administration as an anticancer agent comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

17. A method of treating restenosis comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.

18. A pharmaceutical composition adapted for administration as a restenosis inhibiting agent comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.

19. A solution synthesis method of preparing a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, comprising the preparation of secondary amines and N-substituted amino acids by hydride reduction of an imine formed between an aldehyde and an amine or an amino acid, followed by reaction with an N-substituted histidine or homohistidine derivative, a carbodiimide and 1-hydroxy-benzotriazole.

20. A solid phase synthesis method of preparing a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, comprising simultaneous synthesis of an array of compounds of Formula I in a Diversomer® apparatus, using a D- or L-histidine derivative that is immobilized on a resin via attachment through the imidazole ring with sequential deprotection and acylation of the N-terminus by a series of isocyanates, activated esters, acid chlorides and the like, followed by sequential deprotection of the carboxy terminus, carboxyl activation and condensation with a series of amines and amino acids, followed by cleavage from the solid support.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 95/06660

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/078 C07K5/097 C07D233/64 A61K38/05 A61K38/06 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO-A-94 00419 (DEANA ERMELINDA S & LF ;MERCK & CO INC (US); DESOLMS S JANE (US);) 6 January 1994 see the whole document ---	1-20
A	BIOORG.MED.CHEM.LETT., vol. 4, no. 7, 1994 pages 887-892, K.LEFTHERIS E.A. 'PEPTIDE BASED P21-RAS FARNESYL TRANSFERASE INHIBITORS...' see table 1 ---	1-20
P,X	WO-A-95 09001 (MERCK & CO INC ;DESOLMS S JANE (US); GARSKY VICTOR M (US); GIULIAN) 6 April 1995 see claims 1-3,5-7,16-18,21-23-28 -----	1,2,4, 13-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 1995	06. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Groenendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...information on patent family members

Inter... nal Application No
PCT/US 95/06660

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9400419	06-01-94	US-A-	5352705	04-10-94
		AU-B-	4645593	24-01-94
		CA-A-	2137455	06-01-94
		EP-A-	0664789	02-08-95
WO-A-9509001	06-04-95	AU-B-	7923494	18-04-95

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/06660

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13,15,17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 13,15,17 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.